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1. Document ID: US 5925566 A
Entry 1 of 25 File: USPT Jul 20, 1999

US-PAT-NO: 5925566
DOCUMENT-IDENTIFIER: US 5925566 A
TITLE: Non-activated receptor complex proteins and uses thereof

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

2. Document ID: US 5919905 A
Entry 2 of 25 File: USPT Jul 6, 1999

US-PAT-NO: 5919905
DOCUMENT-IDENTIFIER: US 5919905 A
TITLE: Cytokine designated LERK-6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

3. Document ID: US 5916755 A
Entry 3 of 25 File: USPT Jun 29, 1999

US-PAT-NO: 5916755
DOCUMENT-IDENTIFIER: US 5916755 A
TITLE: Methods of characterizing ligands for the erbB-3 receptor, methods of influencing erbB-3 activities and methods of diagnosing erbB-3-related neoplasm

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

4. Document ID: US 5914237 A
Entry 4 of 25 File: USPT Jun 22, 1999

US-PAT-NO: 5914237
DOCUMENT-IDENTIFIER: US 5914237 A
TITLE: Kinase receptor activation assay

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

5. Document ID: US 5891650 A
Entry 5 of 25 File: USPT Apr 6, 1999

US-PAT-NO: 5891650
DOCUMENT-IDENTIFIER: US 5891650 A
TITLE: Kinase receptor activation assay

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

6. Document ID: US 5869610 A
Entry 6 of 25 File: USPT Feb 9, 1999

US-PAT-NO: 5869610
DOCUMENT-IDENTIFIER: US 5869610 A
TITLE: Hu-B1.219, a novel human hematopoietin receptor

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

7. Document ID: US 5864020 A
Entry 7 of 25 File: USPT Jan 26, 1999

US-PAT-NO: 5864020
DOCUMENT-IDENTIFIER: US 5864020 A
TITLE: HTK ligand

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

8. Document ID: US 5820859 A
Entry 8 of 25 File: USPT Oct 13, 1998

US-PAT-NO: 5820859
DOCUMENT-IDENTIFIER: US 5820859 A
TITLE: Method of targeting a therapeutic agent to cells expressing the erb B-3 receptor

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

9. Document ID: US 5843749 A
Entry 9 of 25 File: USPT Dec 1, 1998

US-PAT-NO: 5843749
DOCUMENT-IDENTIFIER: US 5843749 A
TITLE: Ehk and Ror tyrosine kinases

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

10. Document ID: US 5766863 A
Entry 10 of 25 File: USPT Jun 16, 1998

US-PAT-NO: 5766863
DOCUMENT-IDENTIFIER: US 5766863 A
TITLE: Kinase receptor activation assay

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

11. Document ID: US 5763211 A
Entry 11 of 25 File: USPT Jun 9, 1998

US-PAT-NO: 5763211
DOCUMENT-IDENTIFIER: US 5763211 A
TITLE: Isolated nucleic acid encoding Hu-B1.219, a novel human hematopoietin

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

12. Document ID: US 5753462 A
Entry 12 of 25 File: USPT May 19, 1998

US-PAT-NO: 5753462
DOCUMENT-IDENTIFIER: US 5753462 A
TITLE: Secretion leader trap cloning method

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

13. Document ID: US 5738844 A
Entry 13 of 25 File: USPT Apr 14, 1998

US-PAT-NO: 5738844
DOCUMENT-IDENTIFIER: US 5738844 A
TITLE: Cytokines that bind the cell surface receptor hek

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

14. Document ID: US 5728813 A
Entry 14 of 25 File: USPT Mar 17, 1998

US-PAT-NO: 5728813
DOCUMENT-IDENTIFIER: US 5728813 A
TITLE: Antibodies directed against elk ligand

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

15. Document ID: US 5705349 A
Entry 15 of 25 File: USPT Jan 6, 1998

US-PAT-NO: 5705349
DOCUMENT-IDENTIFIER: US 5705349 A
TITLE: Methods for preparing polynucleotides encoding orphan receptor ligands

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

16. Document ID: US 5670625 A
Entry 16 of 25 File: USPT Sep 23, 1997

US-PAT-NO: 5670625
DOCUMENT-IDENTIFIER: US 5670625 A
TITLE: Elk ligand fusion proteins

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

17. Document ID: US 5627267 A
Entry 17 of 25 File: USPT May 6, 1997

US-PAT-NO: 5627267
DOCUMENT-IDENTIFIER: US 5627267 A
TITLE: Cytokine designated elk ligand

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

18. Document ID: US 5624899 A
Entry 18 of 25 File: USPT Apr 29, 1997

US-PAT-NO: 5624899
DOCUMENT-IDENTIFIER: US 5624899 A
TITLE: Method for using Htk ligand

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

19. Document ID: US 5541085 A
Entry 19 of 25 File: USPT Jul 30, 1996

US-PAT-NO: 5541085
DOCUMENT-IDENTIFIER: US 5541085 A
TITLE: Method for preparing orphan receptor ligands

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

20. Document ID: US 5516658 A
Entry 20 of 25 File: USPT May 14, 1996

US-PAT-NO: 5516658
DOCUMENT-IDENTIFIER: US 5516658 A
TITLE: DNA encoding cytokines that bind the cell surface receptor hek

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Image

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| LIGANDS | 27107 |
| BINDING | 205946 |
| BINDINGS | 5415 |
| DOMAIN | 75375 |
| DOMAINS | 28278 |
| 4 AND (LIGAND ADJ BINDING ADJ DOMAIN) | 25 |

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Document Number 1

Entry 1 of 25 File: USPT Jul 20, 1999

DOCUMENT-IDENTIFIER: US 5925566 A
TITLE: Non-activated receptor complex proteins and uses thereof

BSPR:
The epidermal growth factor receptor (EGF-R) is a transmembrane glycoprotein with an extracellular ligand binding domain and a cytoplasmic tyrosine kinase domain [Ullrich et al., Cell 61, 203 (1990); Schlessinger et al., Neuron 9, 383 (1992)]. Treatment of cells with epidermal growth factor (EGF) causes increased EGF receptor tyrosine kinase activity, i.e., the activated state. Substrates for the activated EGF-R tyrosine kinase include the COOH terminal region of the receptor [Ullrich et al., supra; Schlessinger et al., supra]. The tyrosine phosphorylated EGF receptor binds to modular signaling proteins that contain Src homolog (SH2) or PTB domains [Ullrich et al., supra; Schlessinger et al., supra; Koch et al, Science 252, 668 (1991); Pawson et al., Cell 71, 359 (1992); Kavanaugh et al., Science 266, 1862 (1994); Bork et al., Cell 80, 693 (1995); Kavanaugh et al., Science 268, 1177 (1995)]. However, prior to the formation of the receptor SH2/PTB signaling complex, the non-activated EGF receptor is proposed to interact with other proteins [Ullrich et al., supra; Schlessinger et al., supra]. The identity of proteins within the non-activated EGF-R complex is currently unknown.

BSPR:
A "ZPR1 polypeptide" is an amino acid sequence that includes a zinc finger domain (e.g., the ZF1 and ZF2 domains described herein) that specifically binds to a cytoplasmic domain (e.g., a cytoplasmic tyrosine kinase) of a membrane growth factor (e.g., epidermal growth factor (EGF) receptor, platelet-derived growth factor (PDGF) receptor, and any EPH class of neuronal receptor such as (Eph, Eck, Hek, Erk, Htk). ZPR1 polypeptides also include ZPR1 fusion proteins (e.g., ZPR1-GST) and epitope-tagged ZPR1 polypeptides. ZPR1 polypeptides, in general, have amino acid identity that is at least 30%, preferably 50%, and most preferably 80%, 90%, or even 95% identical to any of the ZPR1 amino acid sequences

including, but not limited to, mammalian sequences from the mouse (FIG. 1; SEQ ID NO:1), rat, or human (FIG. 2; SEQ ID NO:2), and yeast ZPR1 sequences from S. cerevisiae (FIG. 3; SEQ ID NO:3) and S. pombe (FIG. 4; SEQ ID NO:4), which are disclosed herein.

BSPR:
A "modulatory compound" is any compound capable of either increasing or decreasing ZPR1 gene expression (i.e., at the level of transcription, translation, or post-translation), or increasing or decreasing ZPR1 protein activity (i.e., the amount of activity, for example, EGF receptor (or PDGF receptor or EPH receptor) binding activity, per unit of ZPR1 protein).

Document Number 2

Entry 2 of 25 File: USPT Jul 6, 1999

DOCUMENT-IDENTIFIER: US 5919905 A
TITLE: Cytokine designated LERK-6

BSPR:
The present invention relates to cytokine polypeptides designated as LERK-6 that bind to the hek or elk receptor, the nucleic acids encoding such polypeptides, processes for production of recombinant LERK-6 polypeptides, and pharmaceutical compositions containing such polypeptides.

BSPR:
Boyd et al. (J. Biol. Chem., 267:3262, 1992) purified a cell-surface glycoprotein exhibiting tyrosine kinase activity. The amino acid sequence identified this protein as a member of the eph/elk family, and the protein was thus designated hek (human eph/elk-like kinase). A monoclonal antibody immunoreactive with hek was used to study hek expression on a number of human cell types (Boyd et al., supra). Hek antigen was detected on the human pre-B cell leukemia cell line LK63 (the cell line employed as the immunogen against which the antibody was raised) and the human T-cell leukemia cell line, JM. The Raji B lymphoma cell line showed weak hek antigen expression, and the remaining cell lines tested (both normal and tumor cell lines, among which were hemopoietic cell lines that included pre-B and T-cell lines) were consistently negative. Of the normal and tumor tissue biopsy specimens that were also tested for hek antigen expression, none of the normal tissues was positive and only a very low proportion of hemopoietic tumors was positive.

BSPR:
Expression of hek transcripts in the above-described LK63 and JM cell lines, as well as the human T-cell leukemia cell line HSB-2, has been demonstrated by northern blot analysis (Wicks et al., Proc. Natl. Acad. Sci. USA, 89:1611, 1992). Nucleotide and amino acid sequences for an isolated hek cDNA clone are presented in Wicks et al., supra.

BSPR:
The cell surface protein designated elk is another member of the eph-related tyrosine kinase receptor family of proteins. A partial clone of elk was first discovered in a rat brain cDNA expression library that was screened for proteins expressing tyrosine kinase activity (Letwin et al., Oncogene 3:621, 1988). Later, a composite sequence spanning the entire elk coding region was derived from partial clones isolated from a rat brain cDNA library and a rat cerebellar brain library using the partial clone as a probe (Lhotak et al., Mol. Cell. Biol. 11:2496, 1991).

BSPR:
The hek and elk proteins are closely related to a number of other receptor tyrosine kinases, including the hek homologs mek4 and cek4 (Sajjadi et al. New Biol. 3:769, 1991); eek (Chan et al. Oncogene 6:1057, 1991); erk (Chan et al. supra.), eck (Lindberg et al. Mol. Cell. Biol. 10:6316, 1990); cekS (Pasquale, E. B. Cell Regulation 2:523, 1991); and eph (Hirai et al. Science 238:1717, 1987). The proteins of this subfamily are related not only in their cytoplasmic domains, but also in their extracellular domains, which are 41 to 68% identical. Interestingly, the tissue distributions of these various receptors are diverse. For example, expression of elk mRNA has been reported to be limited to testis and brain (Lhotak et al., supra), whereas eck is found not only in these same two tissues but in lung, intestine, kidney, spleen, ovary, and skin as well. In addition, most eph-related receptors are primarily expressed in the brain. Due to the homology of the receptors in the eph family, a given ligand for one specific receptor may also bind other receptors.

BSPR:
Those ligands that have been identified for the receptor tyrosine kinases are a diverse group of proteins that affect the growth, differentiation, and survival of cells expressing the receptors. Ligands for hek and elk have been isolated, as discussed in more detail below.

BSPR:
Identification of additional ligands for hek and elk that may exist would prove useful in investigating the nature of cellular processes regulated by signaling through these receptors. If enhancement or inhibition of a particular biological signal mediated through these receptors is desired, it is advantageous to identify each of the proteins that may play a role in transduction of such signals. Further, it is known that certain proteins can bind to receptors without initiating signal transduction, including interleukin-1 receptor antagonist protein (Eisenberg et al., Nature 343:341, 1990; Hannum et al., Nature 343:336, 1990; and Carter et al., Nature 344:633, 1990). Identification of additional proteins that bind hek or elk is also

desirable in order to determine whether such proteins function as antagonists.

BSPR:
In addition, LERK-6 can be bound to a solid phase matrix and used to affinity-purify or separate cells that express hek or elk on their cell surface. The invention encompasses separating cells having the hek or elk receptor on the surface thereof from a mixture of cells in solution, comprising contacting the cells in the mixture with a contacting surface having a LERK-6 molecule thereon, and separating the contacting surface and the solution.

DEPR:
LERK-6 may be useful in the enhancement, stimulation, proliferation or growth of cells expressing the hek or elk receptor. Since the hek or elk receptor is found in the tissue of the brain and testis, treatment of a variety of conditions associated with tissue damage thereof is possible. Moreover, the ligand and receptor complex may be involved in neural growth, development and/or maintenance. While not limited to such, particular uses of the LERK-6 are described infra.

DEPR:
As used herein, the term "LERK-6" refers to a genus of polypeptides that bind and complex independently with hek or elk receptor found on T-cells and brain cells. The term "LERK-6" encompasses polypeptides having the amino acid sequence 1-184 of SEQ ID NO:2, proteins that are encoded by nucleic acids that contain the nucleic acid sequence of SEQ ID NO:7, and polypeptides having the amino acid sequence 1-184 of SEQ ID NO: 10. In addition, LERK-6 encompasses polypeptides that have a high degree of similarity or a high degree of identity with the amino acid sequence 1-184 of SEQ ID NO:2, the amino acid sequence of SEQ ID NO:8, and amino acids 1-184 of SEQ ID NO: 10, and which polypeptides are biologically active and bind the hek or elk receptor. In addition, the term "murine LERK-6" refers to biologically active gene products of the DNA of SEQ ID NO: I and the term "human LERK-6" refers to biologically active gene products of the DNA of SEQ ID NO:9. Further encompassed by the term "LERK-6" are the GPI-linked proteins (which include an extracellular region and a C-terminal hydrophobic region), and soluble or truncated proteins that comprise primarily the receptor-binding portion of the protein, retain biological activity and are capable of being secreted. Specific examples of such soluble proteins are those comprising the sequence of amino acids 1 (Ala)-145 (Asn) of SEQ ID NO:2 and those comprising the sequence of amino acids 1-145 of SEQ ID NO: 10.

DEPR:
The term "hek/elk" means either hek or elk or both hek

and elk. For example, the term "anti-hek/elk antibodies" refers to antibodies against either hek or elk. The term "hek/elk-expressing cells" refers to cells that express either the hek receptor or the elk receptor, or cells that express both the hek and elk receptors.

DEPR:
As described supra, an aspect of the invention is soluble LERK-6 polypeptides. Soluble LERK-6 polypeptides comprise all or part of the extracellular domain of a native LERK-6 but lack the GPI signal that would cause retention of the polypeptide on a cell membrane. Soluble LERK-6 polypeptides advantageously comprise the native (or a heterologous) signal peptide when initially synthesized to promote secretion, but the signal peptide is cleaved upon secretion of LERK-6 from the cell. Soluble LERK-6 polypeptides encompassed by the invention retain the ability to bind the hek or elk receptor. Indeed, soluble LERK-6 may also include part of the GPI signal or part of the cytoplasmic domain or other sequences, provided that the soluble LERK-6 protein can be secreted.

DEPR:
Variants possessing the requisite ability to bind hek/elk receptor may be identified by any suitable assay. Biological activity of LERK-6 may be determined, for example, by competition for binding to the ligand binding domain of hek/elk receptor (i.e. competitive binding assays).

DEPR:
One type of a competitive binding assay for a LERK-6 polypeptide uses a radiolabeled, soluble LERK-6 and intact hek/elk-expressing cells. Instead of intact cells, one could substitute soluble hek/elk:Fc fusion proteins (such as a hek:Fc or elk:Fc fusion protein) bound to a solid phase through the interaction of a Protein A, Protein G or an antibody to the hek, elk or Fc portions of the molecule, with the Fc region of the fusion protein. Another type of competitive binding assay utilizes radiolabeled soluble hek or elk receptors such as a hek:Fc or elk:Fc fusion protein, and intact cells expressing LERK-6.

DEPR:
The LERK-6 proteins disclosed herein also may be employed to measure the biological activity of elk or hek proteins in terms of their binding affinity for LERK-6. As one example, LERK-6 may be used in determining whether biological activity is retained after modification of an elk or hek protein (e.g., chemical modification, truncation, mutation. etc.). The biological activity of an elk or hek protein thus can be ascertained before it is used in a research study, or possibly in the clinic, for example.

DEPR:
LERK-6 proteins find use as reagents that may be employed by those conducting "quality assurance" studies, e.g., to monitor shelf life and stability of elk protein under different conditions. To illustrate, LERK-6 may be employed in a binding affinity study to measure the biological activity of an elk protein that has been stored at different temperatures, or produced in different cell types. The binding affinity of the modified elk protein for LERK-6 is compared to that of an unmodified elk protein to detect any adverse impact of the modifications on biological activity of elk. Likewise, the biological activity of a hek protein can be assessed using LERK-6.

DEPR:
LERK-6 polypeptides also find use as carriers for delivering agents attached thereto to cells bearing the elk or hek cell surface receptor. Expression of hek antigen has been reported for certain leukemic cell lines, including the human T-cell leukemia cell line designated JM and the human pre-B cell leukemia cell line designated LK63 (Boyd et al., J. Biol. Chem. 267:3262, 1992, and Wicks et al., Proc. Natl. Acad. Sci. USA, 89:1611, 1992). LERK-6 proteins thus can be used to deliver diagnostic or therapeutic agents to these cells (or to other cell types found to express hek on the cell surface) in in vitro or in vivo procedures.

DEPR:
Another use of the LERK-6 of the present invention is as a research tool for studying the role that LERK-6, in conjunction with elk or hek, may play in growth or differentiation of cells bearing the elk or hek receptor. The LERK-6 polypeptides of the present invention also may be employed in in vitro assays for detection of elk or LERK-6 or the interactions thereof. Likewise, LERK-6 finds use in assays for hek or the interaction of LERK-6 with hek.

DEPR:
As discussed above, when various rat tissues were analyzed for elk mRNA, transcripts were detected only in brain and testis (Lhotak et al., supra). Binding of LERK-6 to eph-related receptors on neural tissue is believed to exert a neuro-protective or neurotrophic effect.

DEPR:
LERK-6 polypeptides may exist as oligomers, such as covalently-linked or non-covalently-linked dimers or trimers. Oligomers may be linked by disulfide bonds formed between cysteine residues on different LERK-6 polypeptides. In one embodiment of the invention, a LERK-6 dimer is created by fusing LERK-6 to the Fc region of an antibody (e.g., IgG1) in a manner that does not interfere with binding of LERK-6 to the hek/elk

ligand-binding domain. The Fc polypeptide preferably is fused to the C-terminus of a soluble LERK-6 (comprising only the receptor-binding). General preparation of fusion proteins comprising heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al. (PNAS USA 88:10535, 1991) and Byrn et al. (Nature 344:677, 1990), hereby incorporated by reference. A gene fusion encoding the LERK-6:Fc fusion protein is inserted into an appropriate expression vector. LERK-6:Fc fusion proteins are allowed to assemble much like antibody molecules, whereupon interchain disulfide bonds form between Fc polypeptides, yielding divalent LERK-6. If fusion proteins are made with both heavy and light chains of an antibody, it is possible to form a LERK-6 oligomer with as many as four LERK-6 extracellular regions. Alternatively, one can link two soluble LERK-6 domains with a peptide linker.

DEPR:
It is possible to utilize an affinity column comprising the ligand-binding domain of hek/elk receptors to affinity-purify expressed LERK-6 polypeptides. LERK-6 polypeptides can be removed from an affinity column using conventional techniques, e.g., in a high salt elution buffer and then dialyzed into a lower salt buffer for use or by changing pH or other components depending on the affinity matrix utilized. Alternatively, the affinity column may comprise an antibody that binds LERK-6. Example 5 describes a procedure for employing LERK-6 of the invention to generate monoclonal antibodies directed against LERK-6.

DEPR:
A DNA and encoded amino acid sequence for human hek cDNA is presented in Wicks et al. (Proc. Nat'l. Acad. Sci. USA, 89:1611, 1992), incorporated herein by reference. This hek protein comprises (from N- to C-terminus) an extracellular domain, a transmembrane domain, and a cytoplasmic domain.

DEPR:
Two DNA fragments, one encoding an N-terminal fragment of the extracellular domain of hek and the other encoding a C-terminal fragment of the hek extracellular domain, were isolated by polymerase chain reactions (PCR) conducted under standard conditions, using oligonucleotide primers based on the hek nucleotide sequence published by Wicks et al., supra. The template for the PCR was cDNA prepared from mRNA isolated from a human T-cell leukemic cell line designated CCRF-HSB-2 (ATCC CCL-120.1). The PCR products containing the 5' end of the hek DNA were digested with SpeI and HindIII to isolate a DNA fragment extending from the 5' end of the mature human hek sequence (i.e., lacking DNA encoding the signal sequence) to a HindIII site found in the hek gene. The PCR products containing the 3' end of the hek

extracellular domain DNA were digested with HindIII and ClaI to isolate a fragment extending from the internal HindlII site to a ClaI site just downstream of the 3' end of the sequence encoding the hek extracellular domain. The ClaI site is in a multiple cloning site (mcs) introduced just downstream of the extracellular domain.

DEPR:
A four-way ligation was conducted to insert the two hek-encoding DNA fragments and the Fc mutein-encoding DNA fragment described above into the SpeI/NotI cleaved SMAG4 expression vector. E. coli cells were transfected with the ligation mixture and the desired recombinant vector was isolated therefrom. The isolated vector encodes a fusion protein comprising (from N- to C-terminus) the murine IL-7 signal peptide, the hek extracellular domain, four amino acids encoded by the introduced mcs, and the Fc mutein.

DEPR:
The ability of LERK-6 to bind to elk or hek can be determined by using the following assay. Cells expressing LERK-6 on the cell surface are prepared. LERK-6 DNA is amplified by PCR. The primers employed in the PCR are selected to define the termini of the coding region of the LERK-6 DNA, and also include a Xho I restriction site at the 5' end and a Not I site at the 3' end of the amplified DNA. The 5' primer additionally included a consensus Kozak sequence upstream of the initiation codon.

DEPR:
This example illustrates a method for preparing monoclonal antibodies to LERK-6. Purified LERK-6, a fragment thereof such as the extracellular domain, synthetic peptides or cells that express LERK-6 can be used to generate monoclonal antibodies against LERK-6 using conventional techniques, for example, those techniques described in U.S. Pat. No. 4,411,993. Briefly, mice are immunized with LERK-6 as an immunogen emulsified in complete Freund's adjuvant, and injected in amounts ranging from 10-100 .mu.g subcutaneously or intraperitoneally. Ten to twelve days later, the immunized animals are boosted with additional LERK-6 emulsified in incomplete Freund's adjuvant. Mice are periodically boosted thereafter on a weekly to bi-weekly immunization schedule. Serum samples are periodically taken by retro-orbital bleeding or tail-tip excision to test for LERK-6 antibodies by dot blot assay, ELISA (Enzyme-Linked Immunosorbent Assay) or inhibition of hek or elk binding.

ORPL:
Beckmann, M.P. et al., "Molecular characterization of a family of ligands for eph-related tyrosine kinase receptors", EmBO Journal 13: 3757-3762, 1994.

ORPL:
Carpenter, M.K., et al., "Ligands for EPH-Related Tyrosine Kinase Receptors are Developmentally Regulated in the CNS", Journal of Neuroscience Research 42: 199-206, 1995.

ORPL:
Wicks, I.P., et al., "Molecular cloning of HEK, the gene encoding a receptor tyrosine kinase expressed by human lymphoid tumor cell lines", Proc. Natl. Acad. Sci. 89: 1611-15, 1992.

ORPL:
Tuzi, N.L., et al., "eph, the largest known family of putative growth factor receptors", Br. J. Cancer 69: 417-21, 1994.

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Document Number 3

Entry 3 of 25 File: USPT Jun 29, 1999

DOCUMENT-IDENTIFIER: US 5916755 A
TITLE: Methods of characterizing ligands for the erbB-3 receptor, methods of influencing erbB-3 activities and methods of diagnosing erbB-3-related neoplasm

BSPR:
Proto-oncogenes encoding growth factor receptors constitute several distinct families with close overall structural homology. The highest degree of homology is observed in their catalytic domains, essential for the intrinsic tyrosine kinase activity of these proteins. Examples of such receptor families include: the EGFR and the related product of the erbB-2 oncogene; the Colony Stimulating Factor 1 receptor (CSF-1-R) and the related Platelet-Derived Growth Factor receptor (PDGF-R); the insulin receptor (IR) and the related Insulin-like Growth factor 1 receptor (IGF-1R); and the receptors encoded by the related oncogenes eph and elk.

BSPR:
This invention additionally provides a method of decreasing a biochemical or biological activity mediated by the erbB-3 receptor, comprising blocking the binding of an erbB-3 activating ligand with the erbB-3 receptor. The blocking can be accomplished by an antibody reactive with the ligand binding domain of the erbB-3 receptor or by an erbB-3 blocking ligand. Furthermore, a method of promoting a biochemical or biological activity mediated by the erbB-3 receptor, comprising contacting an erbB-3 activating ligand with the erbB-3 receptor is provided.

DRPR:
FIG. 4. Comparison of the predicted amino acid sequence of the erbB-3 polypeptide with other receptor-like tyrosine kinases. The amino acid sequence is shown in single letter code and is numbered on the right. The putative extracellular domain (light shading) extends between the predicted signal sequence (solid box) at the amino-terminus and a single hydrophobic transmembrane region (solid box) within the polypeptide. The two cysteine clusters (Cys) in the extracellular domain and the predicted tyrosine kinase domain (TK) within the

cytoplasmic portion of the polypeptide are outlined by dark-shading. The putative ATP-binding site at the amino-terminus of the TK domain is circled. Potential autophosphorylation sites within the carboxyl-terminal domain (COOH) are indicated by asterisks. Potential N-linked glycosylation sites (.fwdarw.) are marked above the amino acid sequence. The percentage of amino acid homology of erbB-3 in individual domains with erbB-2, EGFR, met, eph, insulin receptor (IR), and fms is listed below. Less than 16% dentity is denoted by (-);

DEPR:
The putative erbB-3 ligand-binding domain was 43% and 45% identical in amino acid residues with the predicted erbB-2 and EGFR protein, respectively. Within the extracellular domain, all 50 cysteine residues of the processed erbB-3 polypeptide were conserved and similarly spaced when compared to the EGFR and erbB-2. Forty-seven cysteine residues were organized in two clusters containing 22 and 25 cysteines respectively, a structural hallmark of this tyrosine kinase receptor subfamily (see, for example, Yamamoto, T., Ikawa, S., Akiyama, T., Semba, K., Nomura, N., Miyajima, N., Saito, T. and Toyoshima, K., 1986, Nature 319:230-234). Ten potential N-linked glycosylation sites were localized within the erbB-3 extracellular domain. In comparison with the EGFR and erbB-2 proteins, five and two of these glycosylation sites were conserved, respectively. Among these, the site proximal to the transmembrane domain was conserved among all three proteins (SEQ ID NO:4).

DEPR:
To explore erbB-3 signaling, a chimeric receptor, LTR-EGFR/erbB-3, containing the ligand-binding domain of the closely related EGF receptor (aa 1-682) and the intracellular portion of erbB-3 (aa 681-1342) was engineered. Linearized expression constructs (0.01-10 .mu.g/plate) were transfected into NIH/3T3 cells by calcium phosphate precipitation using 40 .mu.g of calf thymus DNA as carrier. Mass cultures expressing the recombinant proteins were obtained by selection with 750 .mu.g/ml G418. Selected LTR-EGFR/erbB-3 transfectants were enriched for expression of the chimeric protein by preparative FACS sorting using EGFR monoclonal antibody AB-1 (Oncogene Sciences).

CLPR:
23. The method of claim 22, wherein the blocking is accomplished by an antibody reactive with the ligand binding domain of the erbB-3 receptor protein.

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Document Number 3

Entry 3 of 25 File: USPT Jun 29, 1999

DOCUMENT-IDENTIFIER: US 5916755 A
TITLE: Methods of characterizing ligands for the erbB-3 receptor, methods of influencing erbB-3 activities and methods of diagnosing erbB-3-related neoplasm

BSPR:
Proto-oncogenes encoding growth factor receptors constitute several distinct families with close overall structural homology. The highest degree of homology is observed in their catalytic domains, essential for the intrinsic tyrosine kinase activity of these proteins. Examples of such receptor families include: the EGFR and the related product of the erbB-2 oncogene; the Colony Stimulating Factor 1 receptor (CSF-1-R) and the related Platelet-Derived Growth Factor receptor (PDGF-R); the insulin receptor (IR) and the related Insulin-like Growth factor 1 receptor (IGF-1R); and the receptors encoded by the related oncogenes eph and elk.

BSPR:
This invention additionally provides a method of decreasing a biochemical or biological activity mediated by the erbB-3 receptor, comprising blocking the binding of an erbB-3 activating ligand with the erbB-3 receptor. The blocking can be accomplished by an antibody reactive with the ligand binding domain of the erbB-3 receptor or by an erbB-3 blocking ligand. Furthermore, a method of promoting a biochemical or biological activity mediated by the erbB-3 receptor, comprising contacting an erbB-3 activating ligand with the erbB-3 receptor is provided.

DRPR:
FIG. 4. Comparison of the predicted amino acid sequence of the erbB-3 polypeptide with other receptor-like tyrosine kinases. The amino acid sequence is shown in single letter code and is numbered on the right. The putative extracellular domain (light shading) extends between the predicted signal sequence (solid box) at the amino-terminus and a single hydrophobic transmembrane region (solid box) within the polypeptide. The two cysteine clusters (Cys) in the extracellular domain and the predicted tyrosine kinase domain (TK) within the

cytoplasmic portion of the polypeptide are outlined by dark-shading. The putative ATP-binding site at the amino-terminus of the TK domain is circled. Potential autophosphorylation sites within the carboxyl-terminal domain (COOH) are indicated by asterisks. Potential N-linked glycosylation sites (.fwdarw.) are marked above the amino acid sequence. The percentage of amino acid homology of erbB-3 in individual domains with erbB-2, EGFR, met, eph, insulin receptor (IR), and fms is listed below. Less than 16% dentity is denoted by (-);

DEPR:
The putative erbB-3 ligand-binding domain was 43% and 45% identical in amino acid residues with the predicted erbB-2 and EGFR protein, respectively. Within the extracellular domain, all 50 cysteine residues of the processed erbB-3 polypeptide were conserved and similarly spaced when compared to the EGFR and erbB-2. Forty-seven cysteine residues were organized in two clusters containing 22 and 25 cysteines respectively, a structural hallmark of this tyrosine kinase receptor subfamily (see, for example, Yamamoto, T., Ikawa, S., Akiyama, T., Semba, K., Nomura, N., Miyajima, N., Saito, T. and Toyoshima, K., 1986, Nature 319:230-234). Ten potential N-linked glycosylation sites were localized within the erbB-3 extracellular domain. In comparison with the EGFR and erbB-2 proteins, five and two of these glycosylation sites were conserved, respectively. Among these, the site proximal to the transmembrane domain was conserved among all three proteins (SEQ ID NO:4).

DEPR:
To explore erbB-3 signaling, a chimeric receptor, LTR-EGFR/erbB-3, containing the ligand-binding domain of the closely related EGF receptor (aa 1-682) and the intracellular portion of erbB-3 (aa 681-1342) was engineered. Linearized expression constructs (0.01-10 .mu.g/plate) were transfected into NIH/3T3 cells by calcium phosphate precipitation using 40 .mu.g of calf thymus DNA as carrier. Mass cultures expressing the recombinant proteins were obtained by selection with 750 .mu.g/ml G418. Selected LTR-EGFR/erbB-3 transfectants were enriched for expression of the chimeric protein by preparative FACS sorting using EGFR monoclonal antibody AB-1 (Oncogene Sciences).

CLPR:
23. The method of claim 22, wherein the blocking is accomplished by an antibody reactive with the ligand binding domain of the erbB-3 receptor protein.

Help Logout

Document Number 9

Entry 9 of 25 File: USPT Dec 1, 1998

DOCUMENT-IDENTIFIER: US 5843749 A
TITLE: Ehk and Ror tyrosine kinases

DEPR:
Sequence data for Rtk-2, shown in FIG. 14 (SEQ ID NOS:77-78), indicates that nucleotides 801-875 appear to code for a transmembrane domain, nucleotides 1002-1850 appear to contain a tyrosine kinase domain; and 1-800 code for a continuous open reading frame comprising a ligand binding domain. A 180 amino acid stretch follows the tyrosine kinase domain, in contrast to trks, which terminate shortly following the tyrosine kinase domain.

ORPL:
Sajjadi, et al, "Five novel avian Eph-related tyrosine kinases are differentially expressed", Oncogene 8, (Jul., 1993), pp. 1807-1813.

Document Number 14

Entry 14 of 25 File: USPT Mar 17, 1998

DOCUMENT-IDENTIFIER: US 5728813 A
TITLE: Antibodies directed against elk ligand

BSPR:
The cell surface protein designated elk is a member of a family of proteins known as the tyrosine kinase receptors. Proteins of this family have an intrinsic kinase activity that is activated upon ligand binding. A partial clone of elk was first discovered in a rat brain cDNA expression library that was screened for proteins expressing tyrosine kinase activity (Letwin et al., Oncogene 3:621, 1988). Later, a composite sequence spanning the entire elk coding region was derived from partial clones isolated from a rat brain cDNA library and a rat cerebellar brain library using the partial clone as a probe (Lhotak et al., Mol. Cell. Biol. 11:2496, 1991). The elk protein is very closely related to a number of other receptor tyrosine kinases, including hek (Boyd et al. J. Biol. Chem. 267:3262, 1992 and Wicks et al. Proc. Natl. Acad. Sci. USA 89:1611, 1992); the hek homologs mek4 and cek4 (Sajjadi et al. New Biol. 3:769, 1991); eek (Chan et al. Oncogene 6:1057, 1991); eek (Chan et al. supra.), eck (Lindberg et al. Mol. Cell. Biol. 10:6316, 1990); cek5 (Pasquale, E. B. Cell Regulation 2:523, 1991); and eph (Hirai et al. Science 238:1717, 1987). The proteins of this subfamily are related not only in their cytoplasmic domains, but also in their extracellular domains, which are 41 to 68% identical. Interestingly, the tissue distributions of these various receptors are diverse. For example, expression of elk mRNA has been shown to be limited to testis and brain (Lhotak et al., supra), whereas eck is found not only in these same two tissues but in lung, intestine, kidney, spleen, ovary, and skin as well.

BSPR:
Variants possessing the requisite ability to bind elk may be identified by any suitable assay. Biological activity of elk-L may be determined, for example, by competition for binding to the ligand binding domain of elk (i.e. competitive binding assays).

BSPR:
Elk-L polypeptides may exist as oligomers, such as dimers or trimers. Oligomers are linked by disulfide bonds formed between cysteine residues on different elk-L polypeptides. In one embodiment of the invention, an elk-L dimer is created by fusing elk-L to the Fc region of an antibody (IgG1) in a manner that does not interfere with binding of elk-L to the elk ligand binding domain. The Fc polypeptide preferably is fused to the C-terminus of a soluble elk-L (comprising only the extracellular domain). Preparation of fusion proteins comprising heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al., (PNAS USA 88:10535, 1991) and Byrn et al., (Nature 344:677, 1990), hereby incorporated by reference. A gene fusion encoding the elk-L/Fc fusion protein is inserted into an appropriate expression vector. The elk-L/Fc fusion proteins are allowed to assemble much like antibody molecules, whereupon interchain disulfide bonds form between Fc polypeptides, yielding divalent elk-L. If fusion proteins are made with both heavy and light chains of an antibody, it is possible to form a elk-L oligomer with as many as four elk-L extracellular regions. Alternatively, one can link two soluble elk-L domains with a peptide linker such as the Gly.sub.4 SerGly.sub.5 Ser linker sequence described in U.S. Pat. No. 5,073,627.

BSPR:
It is also possible to utilize an affinity column comprising the ligand binding domain of elk to affinity-purify expressed elk-L polypeptides. elk-L polypeptides can be removed from an affinity column in a high salt elution buffer and then dialyzed into a lower salt buffer for use. Alternatively, the affinity column may comprise an antibody that binds elk-L. Example 4 describes a procedure for employing the elk-L protein of the present invention to generate monoclonal antibodies directed against elk-L.

DEPR:
The ability of elk-L to bind to a receptor known as "hek" was investigated in the same assay. Hek, like elk, is a member of the eph/elk family of receptor tyrosine kinases. Boyd et al. (J. Biol. Chem. 267:3262, 1992) purified a cell surface glycoprotein exhibiting tyrosine kinase activity. The N-terminal amino acid sequence identified this protein as a member of the eph/elk family, and the protein was thus designated hek (human eph/elk-like kinase). Expression of hek transcripts on the human pre-B cell leukemia cell line LK63 and the human T-cell leukemia cell line JM, as well as on the human T-cell leukemia cell line HSB-2, has been demonstrated by northern blot analysis (Wicks et al., Proc. Natl. Acad. Sci. USA 89:1611, 1992). Nucleotide

and amino acid sequences for an isolated hek cDNA clone are presented in Wicks et al., supra.

DEPR:
Two hek ligand proteins were included in the assay as well. The protein known as B61 (Holzman et al., Mol. Cell. Biol. 10:5830, 1990) was included in the study because of its degree of homology to elk-L (33% identity at the amino acid level).

DEPR:
Expression vector pDC410 containing DNA encoding B61 or a hek-L protein was substituted for the elk-L expression vector in the foregoing assay. Two hek-L proteins designated A2 and C6, which are 38% identical at the amino acid level, are described in co-pending U.S. application Ser. No. 08/161,132, hereby incorporated by reference. DNA and encoded amino acid sequences for the two hek-L proteins are presented in application Ser. No. 08/161,132. Nucleotide and encoded amino acid sequences for B61 cDNA are presented in Holzman et al., supra, hereby incorporated by reference.

DEPR:
The empty vector exhibited no detectable hek/Fc binding. B61 bound hek/Fc with relatively moderate affinity, exhibiting a single affinity class of binding. The binding of hek/Fc to elk-L resulted in a biphasic pattern, indicating two lower-affinity binding components (affinity constants 2.3.times.10.sup.7 M.sup.-1 and 2.9.times.10.sup.6 M.sup.-1). The affinities of the two hek-L proteins for hek/Fc were equivalent and relatively high.

DEPR:
A biphasic pattern of elk/Fc binding was observed for B61 with K.sub.a s of 2.3.times.10.sup.8 M.sup.-1 and 7.0.times.10.sup.7 M.sup.-1. The affinity constant (K.sub.a) shown for elk/Fc binding to transfected cells expressing elk-L matches well with those observed for binding of elk/Fc to the native ligand expressed on various rat neural cell lines. A biphasic pattern of elk/Fc binding is seen for both hek ligands.

DEPR:
The homology of the full length human elk-L, B61, hek ligand A2, and hek ligand C6 proteins (described in Example 5) for one another at the amino acid level are presented in Table III:

DETL:
TABLE I _____ Binding affinity for hek/Fc (Ka)

_____ pDC410 -- B61 5.5 .times. 10.sup.7 M.sup.-1 elk-L 2.3 .times. 10.sup.7 M.sup.-1 ; 2.9 .times. 10.sup.6 M.sup.-1 hek-L A2 2.0 .times. 10.sup.8 M.sup.-1 hek-L C6 2.0 .times. 10.sup.8

M.sup.-1 _____

DETL:
TABLE II _____ Binding affinity for elk/Fc (Ka)
_____ B61 2.3 .times. 10.sup.8 M.sup.-1 ; 7.0 .times. 10.sup.7 M.sup.-1 elk-L 1.08 .times. 10.sup.9 M.sup.-1 hek-L A2 2.7 .times. 10.sup.8 M.sup.-1 ; 3.5 .times. 10.sup.7 M.sup.-1 hek-L C6 1.3 .times. 10.sup.8 M.sup.-1 ; 5.4 .times. 10.sup.7 M.sup.-1 _____

ORPL:
Cerretti et al., "Isolation of cDNAs that Encode Ligands to the Receptor Tyrosine Kinases Hek and Elk: Emergence of a Family of Proteins that are Ligands for the Eph Related Kinases (LERKS)", Abstract for American Assoc. for Cancer Research conference on Growth Factors, Development, and Cancer, held in Interlaken, Switzerland, Mar. 5-11, 1994.

ORPL:
Beckmann et al., "Molecular Characterization of a Family of Ligands for Eph-Related Tyrosine Kinases", Abstract for Keystone Symposium on Inflammation, Growth Regulatory Molecules, and Atherosclerosis, Keystone, CO, Jan. 16-23, 1994.

ORPL:
Letwin et al., "Novel protein-tyrosine kinase cDNAs related to fpslfes and eph cloned using anti-phosphoryrosine antibody", Oncogene 3:621-627, 1988.

ORPL:
Boyd et al., "Isolation and Characterization of a Novel Receptor-type Protein Tyrosine Kinase (hek) from a Human Pre-B Cell Line", J. Biol. Chem. 267:3262-3267, 1992.

ORPL:
Wicks et al., "Molecular cloning of HEK, the gene encoding a receptor tyrosine kinse expressed by human lymphoid tumor cell line", Proc. Natl. Acad. Sci. USA 89:1611-1615, 1992.

ORPL:
Saijadi et al., "Identification of a New eph-Related Receptor Tyrosine Kinase Gene From Mouse and Chicken That Is Developmentally Regulated and Encodes at Least Two Forms of the Receptor", New Biol. 3:769-788, 1991.

ORPL:
Chan and Watt, "eek and erk, new members of the eph subclass of receptor protein-tyrosine kinases", Oncogene 6:1057-1061, 1991.

ORPL:

Pasquale, "Identification of chicken embryo kinase 5, a developmentally regulated receptor-type tyrosine kinase of the Eph family", Cell Regulation 2:523-534, 1991.

ORPL:
Hirai et al., "A Novel Putative Tyrosine Kinase Receptor Encoded by the eph Gene", Science 238:1717-1720, 1987.

ORPL:
Beckmann et al., "Molecular characterization of a family of ligands for eph-related tyrosine kinase receptors", EMBO J. 13:3757-3762, 1994.

ORPL:
Bohme et al., "Cell-Cell Adhesion Mediated by Binding of Membrane-anchored Ligand LERK-2 to the EPH-related Receptor Human Embryonal Kinase 2 Promotes Tyrosine Kinase Activity", J. Biol. Chem. 271:24747-24752, 1996.

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## Search Results -

| Term | Documents |
|---|---|
| LERK7 | 0 |
| LERK7S | 0 |
| LERK7 | 0 |

**Database:** All Databases (USPT + EPAB + JPAB + DWPI + TDBD)

Refine Search: lerk 7

## Search History

| DB Name | Query | Hit Count | Set Name |
|---|---|---|---|
| ALL | lerk7 | 0 | L10 |
| ALL | lerk7 | 0 | L9 |
| ALL | l4 and lerk7 | 0 | L8 |
| ALL | l4 and ligand binding domain | 25 | L7 |
| ALL | l4 and (eck or erk) | 39 | L6 |
| ALL | l4 and epha3 | 0 | L5 |
| ALL | eph or hek | 774 | L4 |
| ALL | lackman-martin.in | 0 | L3 |
| ALL | dottori-mirella.in | 0 | L2 |
| USPT | boyd-andrew-john.in | 0 | L1 |

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 NEWS  3  Aug  9  Expanded CAplus Coverage of US, Japanese, WIPO
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FULL ESTIMATED COST                                     0.63       0.63

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=> s epha3
L1          55 EPHA3

=> s eph or eck or erk or hek or epha3
L2       19553 EPH OR ECK OR ERK OR HEK OR EPHA3
```

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=> s l2 and ligand binding domain#
L3          47 L2 AND LIGAND BINDING DOMAIN#

=> s l2 and lerk7
L4          18 L2 AND LERK7

=> s l3 and lerk7
L5           0 L3 AND LERK7

=> dup rem l1
PROCESSING COMPLETED FOR L1
L6          19 DUP REM L1 (36 DUPLICATES REMOVED)

=> dup rem l3
PROCESSING COMPLETED FOR L3
L7          15 DUP REM L3 (32 DUPLICATES REMOVED)

=> dup rem l4
PROCESSING COMPLETED FOR L4
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L8   ANSWER 1 OF 6  Full-text?  MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   97341193     MEDLINE
DOCUMENT NUMBER:    97341193
TITLE:              Ligand for EPH-related kinase (LERK) 7 is the
                    preferred high affinity ligand for the HEK
                    receptor.
AUTHOR:             Lackmann M; Mann R J; Kravets L; Smith F M; Bucci T A;
                    Maxwell K F; Howlett G J; Olsson J E; Vanden Bos T;
                    Cerretti D P; Boyd A W
CORPORATE SOURCE:   Cooperative Research Centre for Cellular Growth Factors,
                    Victoria 3050, Australia.
SOURCE:             JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jun 27) 272 (26)
                    16521-30.
                    Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY:       United States
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals; Cancer Journals
ENTRY MONTH:        199709
ENTRY WEEK:         19970903
AB   HEK is a member of the EPH-like receptor tyrosine
     kinase family, which appear to have roles in development and oncogenesis.
     Recently, we purified a soluble HEK ligand which is also a
     ligand (AL1) for the HEK-related receptor EHK1. Promiscuity
     appears to be a characteristic feature of interactions between the
     EPH-like receptors and their ligands, termed ligands for
     EPH-related kinases (LERKs). This prompted us to analyze the
     interactions between the HEK exodomain and fusion proteins
     comprising candidate LERKs and the Fc portion of human IgG1 (Fc) or a
     FLAGTM-peptide tag by surface plasmon resonance, size exclusion high
     performance liquid chromatography, sedimentation equilibrium, and
     transphosphorylation. Our results indicate that AL1/LERK7 is the
     preferred high-affinity ligand for HEK, forming a stable 1:1
     complex with a dissociation constant of 12 nM. As expected the apparent
     affinities of bivalent fusion proteins of LERKs and the Fc portion of
     human IgG1 had significantly reduced dissociation rates compared with
     their monovalent, FLAGTM-tagged derivatives. High-avidity binding of
     monovalent ligands can be achieved by antibody-mediated cross-linking of
     monovalent ligands and with LERK7 results in specific
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phosphorylation of the receptor. By extrapolation, our findings indicate that some of the reported LERK-receptor interactions are a consequence of the use of bivalent ligand or receptor constructs and may be functionally irrelevant.

L8 ANSWER 2 OF 6 Full-text? CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:553254 CAPLUS
DOCUMENT NUMBER: 127:275908
TITLE: LERK-7: a ligand of the **eph**-related kinases is developmentally regulated in the brain
AUTHOR(S): Kozlosky, Carl J.; VandenBos, Tim; Park, Linda; Cerretti, Douglas Pat; Carpenter, Melissa K.
CORPORATE SOURCE: Departments Molecular Biology, Immunex Research Development Corporation, Seattle, WA, 98101, USA
SOURCE: Cytokine (1997), 9(8), 540-549
CODEN: CYTIE9; ISSN: 1043-4666
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **eph** family is the largest subfamily of receptor tyrosine kinases (RTKs). Members of this subfamily display specific expression in the developing and adult brain. Recently, cDNAs encoding membrane bound ligands for these receptors have been identified which the authors have termed LERKs (ligands for **eph**-related kinases). The authors report here the isolation of LERK-7 from a human fetal brain cDNA library. LERK-7 encodes a protein of 228 amino acids and is anchored to the membrane by glycosyl-phosphatidylinositol (GPI) linkage. When transfected into CV1/EBNA cells, LERK-7 binds sol. forms of both **hek** and elk. In addn., a sol. form of LERK-7 will induce phosphorylation of **eck** expressed in a human duodenum adenocarcinoma cell line. LERK-7 expressed multiple transcripts (7.5-kb, 6.0-kb, and 3.5-kb) with the highest levels in human adult brain, heart, spleen, and ovary and human fetal brain, lung, and kidney. Similar to the other ligands in this family, LERK-7 is developmentally regulated in the brain LERK-7 is identical to the recently described AL-1.

L8 ANSWER 3 OF 6 Full-text? MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97465853 MEDLINE
DOCUMENT NUMBER: 97465853
TITLE: Regulation of topographic projection by the **Eph** family receptor Bsk (EphA5) and its ligands.
AUTHOR: Zhou R
CORPORATE SOURCE: Laboratory for Cancer Research, College of Pharmacy, Rutgers University, Piscataway, NJ 08855, USA..
rzhou@rci.rutgers.edu
SOURCE: CELL AND TISSUE RESEARCH, (1997 Nov) 290 (2) 251-9. Ref: 69
Journal code: CQD. ISSN: 0302-766X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104
AB Topographic projection is a general feature of brain architecture and is critical for appropriate information processing and coding. Nevertheless, little is known about the mechanisms that govern topographic organization. The **Eph** family receptor tyrosine kinases and ligands have recently been implicated in the specification of topographic maps. We have shown that Bsk, an **Eph** family receptor, and its ligands are expressed in a complementary fashion in neurons and targets, respectively,

in several neural systems. For example, in the hippocampus, Bsk is expressed in an increasing lateral to medial gradient. In contrast, at least three different ligands, viz., Elf-1, LERK3/Ehk1-L, and AL-1/RAGS/**LERK7**, are transcribed in complementary (opposing) gradients in the hippocampal subcortical target, the lateral septum. However, the spatial and temporal distribution of the ligands are different, such that combinatorially they specify the full target region during development. Consistent with a key role in hippocamposeptal topographic projection, the ligands selectively inhibit the growth of the topographically inappropriate medial hippocampal neurites but sustain the growth of the appropriate lateral neurites. Our studies indicate that the interaction of Bsk and its ligands restricts the receptor-positive medial neurons to the topographically appropriate, ligand-poor dorsal septal target. In addition to the hippocamposeptal system, Bsk and its ligands are also expressed in afferents and targets of several other systems, including the olfactory and the retinotectal systems. Consequently, Bsk and its ligands may play important roles in neuron-target interactions in multiple neural circuits.

L8 ANSWER 4 OF 6 Full-text? CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:483677 CAPLUS
DOCUMENT NUMBER: 125:140562
TITLE: Cytokine designated Lerk-7 and monoclonal antibody against Lerk-7
INVENTOR(S): Cerretti, Douglas P.
PATENT ASSIGNEE(S): Immunex Corporation, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9617925 | A1 | 19960613 | WO 1995-US15781 | 19951205 |
| W: AU, CA, FI, JP, KR, MX, NO, NZ | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2206488 | AA | 19960613 | CA 1995-2206488 | 19951205 |
| AU 9646393 | A1 | 19960626 | AU 1996-46393 | 19951205 |
| EP 871702 | A1 | 19981021 | EP 1995-944314 | 19951205 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE | | | | |
| JP 10512440 | T2 | 19981202 | JP 1995-517719 | 19951205 |
| NO 9702455 | A | 19970806 | NO 1997-2455 | 19970529 |
| FI 9702390 | A | 19970605 | FI 1997-2390 | 19970605 |
| PRIORITY APPLN. INFO.: | | | US 1994-351025 | 19941206 |
| | | | US 1995-396946 | 19950301 |
| | | | WO 1995-US15781 | 19951205 |

AB The invention is directed to a protein designated Lerk-7, DNA encoding the Lerk-7, and host cells transformed with Lerk-7 DNA. Antibodies directed against Lerk-7 are also provided. The Lerk-7 protein binds to the cell surface receptors known as elk and **hek**. Demonstrated in examples were cloning of human Lerk-7 cDNA, prepn. of sol. elk:Fc fusion protein, prepn. of monoclonal antibodies that bind Lerk-7, characterization of binding of Lerk-7 to elk or **hek**, etc.

L8 ANSWER 5 OF 6 Full-text? MEDLINE DUPLICATE 3
ACCESSION NUMBER: 97083705 MEDLINE
DOCUMENT NUMBER: 97083705
TITLE: Detection of ligands in regions anatomically connected to neurons expressing the **Eph** receptor Bsk: potential roles in neuron-target interaction.
AUTHOR: Zhang J H; Cerretti D P; Yu T; Flanagan J G; Zhou R
CORPORATE SOURCE: Department of Chemical Biology, College of Pharmacy, Rutgers University, Piscataway, New Jersey 08855, USA.

SOURCE: JOURNAL OF NEUROSCIENCE, (1996 Nov 15) 16 (22) 7182-92.
Journal code: JDF. ISSN: 0270-6474.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702

AB Neuron-target interaction is a key feature in the establishment of neuronal networks. However, the underlying mechanism remains unclear. We have shown that at the time of target innervation, Bsk, an **eph** family receptor, is expressed at high levels in several brain regions including the hippocampus, olfactory bulb, and retina. To study whether the ligands are expressed in the target tissues, we investigated the expression of Bsk ligands using a ligand-affinity probe, Bsk-AP, which consisted of the extracellular domain of Bsk fused in frame with a human placental alkaline phosphatase. These analyses showed that the ligands were expressed at high levels in the developing septum, hypothalamus, olfactory neural epithelium, and tectum. In situ hybridization studies revealed that at least three different factors were responsible for the Bsk-AP binding. In the septum, Elf-1, Lerk3 (Eff-2), and AL-1/**Lerk7** were transcribed. In the hypothalamus, AL-1/**Lerk7** was the ligand detected by Bsk-AP. In the olfactory system, high levels of Lerk3 were detected in the sensory neurons. Both Elf-1 and AL-1/**Lerk7** were present in the tectum. These ligand-positive areas are known to be anatomically connected to Bsk-expressing regions. These observations strongly suggest that Bsk and the ligands participate in neuron-target interactions in multiple systems and provide support for their involvement in topographic projection.

L8 ANSWER 6 OF 6 Full-text? CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:462898 CAPLUS
DOCUMENT NUMBER: 125:159918
TITLE: The gene encoding LERK-7 (EPLG7, EpI7), a ligand for the **Eph**-related receptor tyrosine kinases, maps to human chromosome 5 at band q21 and to mouse chromosome 17
AUTHOR(S): Cerretti, Douglas Pat; Copeland, Neal G.; Gilbert, Debra J.; Jenkins, Nancy A.; Kuefer, Martin U.; Valentine, Virginia; Shapiro, Daavid N.; Cui, Xiaoli; Morris, Stephan W.
CORPORATE SOURCE: Department Molecular Biology, Immunex Corporation, Seattle, WA, 98101, USA
SOURCE: Genomics (1996), 35(2), 376-379
CODEN: GNMCEP; ISSN: 0888-7543
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **eph**-related receptors are the largest subfamily of receptor tyrosine kinases. Recently, we and others have identified seven different, but related, cDNAs encoding membrane-bound ligands for this family of receptors. One member, LERK-7, is attached to the cell membrane via glycosyl-phosphatidylinositol linkage and has been found to be a ligand for the **eph**-family receptors **hek**, elk, **eck**, and rek. Using PCR-based screening of human .times. rodent somatic cell hybrid DNAs, we have assigned the gene that encodes LERK-7 (EPLG7) to human chromosome 5. Fluorescence in situ hybridization to metaphase chromosome prepns. using a genomic clone from the locus refined this localization to chromosome 5, band q21. In addn., Southern blot anal. of DNAs from interspecific backcross mice indicated that the mouse homolog Epl7 maps to a homologous region on chromosome 17.

=> **d ibib abs 1-15**

L8 ANSWER 1 OF 6 Full-text? MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97341193 MEDLINE
DOCUMENT NUMBER: 97341193
TITLE: Ligand for **EPH**-related kinase (LERK) 7 is the preferred high affinity ligand for the **HEK** receptor.
AUTHOR: Lackmann M; Mann R J; Kravets L; Smith F M; Bucci T A; Maxwell K F; Howlett G J; Olsson J E; Vanden Bos T; Cerretti D P; Boyd A W
CORPORATE SOURCE: Cooperative Research Centre for Cellular Growth Factors, Victoria 3050, Australia.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jun 27) 272 (26) 16521-30.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199709
ENTRY WEEK: 19970903

AB **HEK** is a member of the **EPH**-like receptor tyrosine kinase family, which appear to have roles in development and oncogenesis. Recently, we purified a soluble **HEK** ligand which is also a ligand (AL1) for the **HEK**-related receptor EHK1. Promiscuity appears to be a characteristic feature of interactions between the **EPH**-like receptors and their ligands, termed ligands for **EPH**-related kinases (LERKs). This prompted us to analyze the interactions between the **HEK** exodomain and fusion proteins comprising candidate LERKs and the Fc portion of human IgG1 (Fc) or a FLAGTM-peptide tag by surface plasmon resonance, size exclusion high performance liquid chromatography, sedimentation equilibrium, and transphosphorylation. Our results indicate that AL1/**LERK7** is the preferred high-affinity ligand for **HEK**, forming a stable 1:1 complex with a dissociation constant of 12 nM. As expected the apparent affinities of bivalent fusion proteins of LERKs and the Fc portion of human IgG1 had significantly reduced dissociation rates compared with their monovalent, FLAGTM-tagged derivatives. High-avidity binding of monovalent ligands can be achieved by antibody-mediated cross-linking of monovalent ligands and with **LERK7** results in specific phosphorylation of the receptor. By extrapolation, our findings indicate that some of the reported LERK-receptor interactions are a consequence of the use of bivalent ligand or receptor constructs and may be functionally irrelevant.

L8 ANSWER 2 OF 6 Full-text? CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:553254 CAPLUS
DOCUMENT NUMBER: 127:275908
TITLE: LERK-7: a ligand of the **eph**-related kinases is developmentally regulated in the brain
AUTHOR(S): Kozlosky, Carl J.; VandenBos, Tim; Park, Linda; Cerretti, Douglas Pat; Carpenter, Melissa K.
CORPORATE SOURCE: Departments Molecular Biology, Immunex Research Development Corporation, Seattle, WA, 98101, USA
SOURCE: Cytokine (1997), 9(8), 540-549
CODEN: CYTIE9; ISSN: 1043-4666
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **eph** family is the largest subfamily of receptor tyrosine kinases (RTKs). Members of this subfamily display specific expression in the developing and adult brain. Recently, cDNAs encoding membrane bound ligands for these receptors have been identified which the authors have termed LERKs (ligands for **eph**-related kinases). The authors

report here the isolation of LERK-7 from a human fetal brain cDNA library. LERK-7 encodes a protein of 228 amino acids and is anchored to the membrane by glycosyl-phosphatidylinositol (GPI) linkage. When transfected into CV1/EBNA cells, LERK-7 binds sol. forms of both **hek** and elk. In addn., a sol. form of LERK-7 will induce phosphorylation of **eck** expressed in a human duodenum adenocarcinoma cell line. LERK-7 expressed multiple transcripts (7.5-kb, 6.0-kb, and 3.5-kb) with the highest levels in human adult brain, heart, spleen, and ovary and human fetal brain, lung, and kidney. Similar to the other ligands in this family, LERK-7 is developmentally regulated in the brain LERK-7 is identical to the recently described AL-1.

L8 ANSWER 3 OF 6 Full-text? MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97465853 MEDLINE
DOCUMENT NUMBER: 97465853
TITLE: Regulation of topographic projection by the **Eph** family receptor Bsk (EphA5) and its ligands.
AUTHOR: Zhou R
CORPORATE SOURCE: Laboratory for Cancer Research, College of Pharmacy, Rutgers University, Piscataway, NJ 08855, USA..
rzhou@rci.rutgers.edu
SOURCE: CELL AND TISSUE RESEARCH, (1997 Nov) 290 (2) 251-9. Ref: 69
Journal code: CQD. ISSN: 0302-766X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104

AB Topographic projection is a general feature of brain architecture and is critical for appropriate information processing and coding. Nevertheless, little is known about the mechanisms that govern topographic organization. The **Eph** family receptor tyrosine kinases and ligands have recently been implicated in the specification of topographic maps. We have shown that Bsk, an **Eph** family receptor, and its ligands are expressed in a complementary fashion in neurons and targets, respectively, in several neural systems. For example, in the hippocampus, Bsk is expressed in an increasing lateral to medial gradient. In contrast, at least three different ligands, viz., Elf-1, LERK3/Ehk1-L, and AL-1/RAGS/**LERK7**, are transcribed in complementary (opposing) gradients in the hippocampal subcortical target, the lateral septum. However, the spatial and temporal distribution of the ligands are different, such that combinatorially they specify the full target region during development. Consistent with a key role in hippocamposeptal topographic projection, the ligands selectively inhibit the growth of the topographically inappropriate medial hippocampal neurites but sustain the growth of the appropriate lateral neurites. Our studies indicate that the interaction of Bsk and its ligands restricts the receptor-positive medial neurons to the topographically appropriate, ligand-poor dorsal septal target. In addition to the hippocamposeptal system, Bsk and its ligands are also expressed in afferents and targets of several other systems, including the olfactory and the retinotectal systems. Consequently, Bsk and its ligands may play important roles in neuron-target interactions in multiple neural circuits.

L8 ANSWER 4 OF 6 Full-text? CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:483677 CAPLUS
DOCUMENT NUMBER: 125:140562
TITLE: Cytokine designated Lerk-7 and monoclonal antibody against Lerk-7
INVENTOR(S): Cerretti, Douglas P.

PATENT ASSIGNEE(S): Immunex Corporation, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9617925 | A1 | 19960613 | WO 1995-US15781 | 19951205 |
| W: AU, CA, FI, JP, KR, MX, NO, NZ | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2206488 | AA | 19960613 | CA 1995-2206488 | 19951205 |
| AU 9646393 | A1 | 19960626 | AU 1996-46393 | 19951205 |
| EP 871702 | A1 | 19981021 | EP 1995-944314 | 19951205 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE | | | | |
| JP 10512440 | T2 | 19981202 | JP 1995-517719 | 19951205 |
| NO 9702455 | A | 19970806 | NO 1997-2455 | 19970529 |
| FI 9702390 | A | 19970605 | FI 1997-2390 | 19970605 |
| PRIORITY APPLN. INFO.: | | | US 1994-351025 | 19941206 |
| | | | US 1995-396946 | 19950301 |
| | | | WO 1995-US15781 | 19951205 |

AB The invention is directed to a protein designated Lerk-7, DNA encoding the Lerk-7, and host cells transformed with Lerk-7 DNA. Antibodies directed against Lerk-7 are also provided. The Lerk-7 protein binds to the cell surface receptors known as elk and **hek**. Demonstrated in examples were cloning of human Lerk-7 cDNA, prepn. of sol. elk:Fc fusion protein, prepn. of monoclonal antibodies that bind Lerk-7, characterization of binding of Lerk-7 to elk or **hek**, etc.

L8 ANSWER 5 OF 6 Full-text? MEDLINE DUPLICATE 3
ACCESSION NUMBER: 97083705 MEDLINE
DOCUMENT NUMBER: 97083705
TITLE: Detection of ligands in regions anatomically connected to neurons expressing the **Eph** receptor Bsk: potential roles in neuron-target interaction.
AUTHOR: Zhang J H; Cerretti D P; Yu T; Flanagan J G; Zhou R
CORPORATE SOURCE: Department of Chemical Biology, College of Pharmacy, Rutgers University, Piscataway, New Jersey 08855, USA.
SOURCE: JOURNAL OF NEUROSCIENCE, (1996 Nov 15) 16 (22) 7182-92.
Journal code: JDF. ISSN: 0270-6474.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702

AB Neuron-target interaction is a key feature in the establishment of neuronal networks. However, the underlying mechanism remains unclear. We have shown that at the time of target innervation, Bsk, an **eph** family receptor, is expressed at high levels in several brain regions including the hippocampus, olfactory bulb, and retina. To study whether the ligands are expressed in the target tissues, we investigated the expression of Bsk ligands using a ligand-affinity probe, Bsk-AP, which consisted of the extracellular domain of Bsk fused in frame with a human placental alkaline phosphatase. These analyses showed that the ligands were expressed at high levels in the developing septum, hypothalamus, olfactory neural epithelium, and tectum. In situ hybridization studies revealed that at least three different factors were responsible for the Bsk-AP binding. In the septum, Elf-1, Lerk3 (Eff-2), and AL-1/**Lerk7** were transcribed. In the hypothalamus, AL-1/**Lerk7** was the ligand detected by Bsk-AP. In the olfactory system, high levels of Lerk3 were detected in the sensory neurons. Both Elf-1 and AL-1/**Lerk7** were present in the tectum. These ligand-positive areas are

known to be anatomically connected to Bsk-expressing regions. These observations strongly suggest that Bsk and the ligands participate in neuron-target interactions in multiple systems and provide support for their involvement in topographic projection.

L8 ANSWER 6 OF 6 Full-text? CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:462898 CAPLUS
DOCUMENT NUMBER: 125:159918
TITLE: The gene encoding LERK-7 (EPLG7, EpI7), a ligand for the **Eph**-related receptor tyrosine kinases, maps to human chromosome 5 at band q21 and to mouse chromosome 17
AUTHOR(S): Cerretti, Douglas Pat; Copeland, Neal G.; Gilbert, Debra J.; Jenkins, Nancy A.; Kuefer, Martin U.; Valentine, Virginia; Shapiro, Daavid N.; Cui, Xiaoli; Morris, Stephan W.
CORPORATE SOURCE: Department Molecular Biology, Immunex Corporation, Seattle, WA, 98101, USA
SOURCE: Genomics (1996), 35(2), 376-379
CODEN: GNMCEP; ISSN: 0888-7543
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **eph**-related receptors are the largest subfamily of receptor tyrosine kinases. Recently, we and others have identified seven different, but related, cDNAs encoding membrane-bound ligands for this family of receptors. One member, LERK-7, is attached to the cell membrane via glycosyl-phosphatidylinositol linkage and has been found to be a ligand for the **eph**-family receptors **hek**, elk, **eck**, and rek. Using PCR-based screening of human .times. rodent somatic cell hybrid DNAs, we have assigned the gene that encodes LERK-7 (EPLG7) to human chromosome 5. Fluorescence in situ hybridization to metaphase chromosome prepns. using a genomic clone from the locus refined this localization to chromosome 5, band q21. In addn., Southern blot anal. of DNAs from interspecific backcross mice indicated that the mouse homolog Epl7 maps to a homologous region on chromosome 17.

=> **d ibib abs 1-6**

L8 ANSWER 1 OF 6 Full-text? MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97341193 MEDLINE
DOCUMENT NUMBER: 97341193
TITLE: Ligand for **EPH**-related kinase (LERK) 7 is the preferred high affinity ligand for the **HEK** receptor.
AUTHOR: Lackmann M; Mann R J; Kravets L; Smith F M; Bucci T A; Maxwell K F; Howlett G J; Olsson J E; Vanden Bos T; Cerretti D P; Boyd A W
CORPORATE SOURCE: Cooperative Research Centre for Cellular Growth Factors, Victoria 3050, Australia.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jun 27) 272 (26) 16521-30.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199709
ENTRY WEEK: 19970903
AB **HEK** is a member of the **EPH**-like receptor tyrosine kinase family, which appear to have roles in development and oncogenesis. Recently, we purified a soluble **HEK** ligand which is also a ligand (AL1) for the **HEK**-related receptor EHK1. Promiscuity

appears to be a characteristic feature of interactions between the **EPH**-like receptors and their ligands, termed ligands for **EPH**-related kinases (LERKs). This prompted us to analyze the interactions between the **HEK** exodomain and fusion proteins comprising candidate LERKs and the Fc portion of human IgG1 (Fc) or a FLAGTM-peptide tag by surface plasmon resonance, size exclusion high performance liquid chromatography, sedimentation equilibrium, and transphosphorylation. Our results indicate that AL1/**LERK7** is the preferred high-affinity ligand for **HEK**, forming a stable 1:1 complex with a dissociation constant of 12 nM. As expected the apparent affinities of bivalent fusion proteins of LERKs and the Fc portion of human IgG1 had significantly reduced dissociation rates compared with their monovalent, FLAGTM-tagged derivatives. High-avidity binding of monovalent ligands can be achieved by antibody-mediated cross-linking of monovalent ligands and with **LERK7** results in specific phosphorylation of the receptor. By extrapolation, our findings indicate that some of the reported LERK-receptor interactions are a consequence of the use of bivalent ligand or receptor constructs and may be functionally irrelevant.

L8 ANSWER 2 OF 6 Full-text? CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:553254 CAPLUS
DOCUMENT NUMBER: 127:275908
TITLE: LERK-7: a ligand of the **eph**-related kinases is developmentally regulated in the brain
AUTHOR(S): Kozlosky, Carl J.; VandenBos, Tim; Park, Linda; Cerretti, Douglas Pat; Carpenter, Melissa K.
CORPORATE SOURCE: Departments Molecular Biology, Immunex Research Development Corporation, Seattle, WA, 98101, USA
SOURCE: Cytokine (1997), 9(8), 540-549
CODEN: CYTIE9; ISSN: 1043-4666
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **eph** family is the largest subfamily of receptor tyrosine kinases (RTKs). Members of this subfamily display specific expression in the developing and adult brain. Recently, cDNAs encoding membrane bound ligands for these receptors have been identified which the authors have termed LERKs (ligands for **eph**-related kinases). The authors report here the isolation of LERK-7 from a human fetal brain cDNA library. LERK-7 encodes a protein of 228 amino acids and is anchored to the membrane by glycosyl-phosphatidylinositol (GPI) linkage. When transfected into CV1/EBNA cells, LERK-7 binds sol. forms of both **hek** and elk. In addn., a sol. form of LERK-7 will induce phosphorylation of **eck** expressed in a human duodenum adenocarcinoma cell line. LERK-7 expressed multiple transcripts (7.5-kb, 6.0-kb, and 3.5-kb) with the highest levels in human adult brain, heart, spleen, and ovary and human fetal brain, lung, and kidney. Similar to the other ligands in this family, LERK-7 is developmentally regulated in the brain LERK-7 is identical to the recently described AL-1.

L8 ANSWER 3 OF 6 Full-text? MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97465853 MEDLINE
DOCUMENT NUMBER: 97465853
TITLE: Regulation of topographic projection by the **Eph** family receptor Bsk (EphA5) and its ligands.
AUTHOR: Zhou R
CORPORATE SOURCE: Laboratory for Cancer Research, College of Pharmacy, Rutgers University, Piscataway, NJ 08855, USA..
rzhou@rci.rutgers.edu
SOURCE: CELL AND TISSUE RESEARCH, (1997 Nov) 290 (2) 251-9. Ref: 69
Journal code: CQD. ISSN: 0302-766X.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104

AB Topographic projection is a general feature of brain architecture and is critical for appropriate information processing and coding. Nevertheless, little is known about the mechanisms that govern topographic organization. The **Eph** family receptor tyrosine kinases and ligands have recently been implicated in the specification of topographic maps. We have shown that Bsk, an **Eph** family receptor, and its ligands are expressed in a complementary fashion in neurons and targets, respectively, in several neural systems. For example, in the hippocampus, Bsk is expressed in an increasing lateral to medial gradient. In contrast, at least three different ligands, viz., Elf-1, LERK3/Ehk1-L, and AL-1/RAGS/ **LERK7**, are transcribed in complementary (opposing) gradients in the hippocampal subcortical target, the lateral septum. However, the spatial and temporal distribution of the ligands are different, such that combinatorially they specify the full target region during development. Consistent with a key role in hippocamposeptal topographic projection, the ligands selectively inhibit the growth of the topographically inappropriate medial hippocampal neurites but sustain the growth of the appropriate lateral neurites. Our studies indicate that the interaction of Bsk and its ligands restricts the receptor-positive medial neurons to the topographically appropriate, ligand-poor dorsal septal target. In addition to the hippocamposeptal system, Bsk and its ligands are also expressed in afferents and targets of several other systems, including the olfactory and the retinotectal systems. Consequently, Bsk and its ligands may play important roles in neuron-target interactions in multiple neural circuits.

L8 ANSWER 4 OF 6 Full-text? CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:483677 CAPLUS
DOCUMENT NUMBER: 125:140562
TITLE: Cytokine designated Lerk-7 and monoclonal antibody against Lerk-7
INVENTOR(S): Cerretti, Douglas P.
PATENT ASSIGNEE(S): Immunex Corporation, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9617925 | A1 | 19960613 | WO 1995-US15781 | 19951205 |
| W: AU, CA, FI, JP, KR, MX, NO, NZ | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2206488 | AA | 19960613 | CA 1995-2206488 | 19951205 |
| AU 9646393 | A1 | 19960626 | AU 1996-46393 | 19951205 |
| EP 871702 | A1 | 19981021 | EP 1995-944314 | 19951205 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE | | | | |
| JP 10512440 | T2 | 19981202 | JP 1995-517719 | 19951205 |
| NO 9702455 | A | 19970806 | NO 1997-2455 | 19970529 |
| FI 9702390 | A | 19970605 | FI 1997-2390 | 19970605 |
| PRIORITY APPLN. INFO.: | | | US 1994-351025 | 19941206 |
| | | | US 1995-396946 | 19950301 |
| | | | WO 1995-US15781 | 19951205 |

AB The invention is directed to a protein designated Lerk-7, DNA encoding the Lerk-7, and host cells transformed with Lerk-7 DNA. Antibodies directed

against Lerk-7 are also provided. The Lerk-7 protein binds to the cell surface receptors known as elk and **hek**. Demonstrated in examples were cloning of human Lerk-7 cDNA, prepn. of sol. elk:Fc fusion protein, prepn. of monoclonal antibodies that bind Lerk-7, characterization of binding of Lerk-7 to elk or **hek**, etc.

L8 ANSWER 5 OF 6 Full-text? MEDLINE DUPLICATE 3
ACCESSION NUMBER: 97083705 MEDLINE
DOCUMENT NUMBER: 97083705
TITLE: Detection of ligands in regions anatomically connected to neurons expressing the **Eph** receptor Bsk: potential roles in neuron-target interaction.
AUTHOR: Zhang J H; Cerretti D P; Yu T; Flanagan J G; Zhou R
CORPORATE SOURCE: Department of Chemical Biology, College of Pharmacy, Rutgers University, Piscataway, New Jersey 08855, USA.
SOURCE: JOURNAL OF NEUROSCIENCE, (1996 Nov 15) 16 (22) 7182-92. Journal code: JDF. ISSN: 0270-6474.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702

AB Neuron-target interaction is a key feature in the establishment of neuronal networks. However, the underlying mechanism remains unclear. We have shown that at the time of target innervation, Bsk, an **eph** family receptor, is expressed at high levels in several brain regions including the hippocampus, olfactory bulb, and retina. To study whether the ligands are expressed in the target tissues, we investigated the expression of Bsk ligands using a ligand-affinity probe, Bsk-AP, which consisted of the extracellular domain of Bsk fused in frame with a human placental alkaline phosphatase. These analyses showed that the ligands were expressed at high levels in the developing septum, hypothalamus, olfactory neural epithelium, and tectum. In situ hybridization studies revealed that at least three different factors were responsible for the Bsk-AP binding. In the septum, Elf-1, Lerk3 (Eff-2), and AL-1/**Lerk7** were transcribed. In the hypothalamus, AL-1/**Lerk7** was the ligand detected by Bsk-AP. In the olfactory system, high levels of Lerk3 were detected in the sensory neurons. Both Elf-1 and AL-1/**Lerk7** were present in the tectum. These ligand-positive areas are known to be anatomically connected to Bsk-expressing regions. These observations strongly suggest that Bsk and the ligands participate in neuron-target interactions in multiple systems and provide support for their involvement in topographic projection.

L8 ANSWER 6 OF 6 Full-text? CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:462898 CAPLUS
DOCUMENT NUMBER: 125:159918
TITLE: The gene encoding LERK-7 (EPLG7, EpI7), a ligand for the **Eph**-related receptor tyrosine kinases, maps to human chromosome 5 at band q21 and to mouse chromosome 17
AUTHOR(S): Cerretti, Douglas Pat; Copeland, Neal G.; Gilbert, Debra J.; Jenkins, Nancy A.; Kuefer, Martin U.; Valentine, Virginia; Shapiro, Daavid N.; Cui, Xiaoli; Morris, Stephan W.
CORPORATE SOURCE: Department Molecular Biology, Immunex Corporation, Seattle, WA, 98101, USA
SOURCE: Genomics (1996), 35(2), 376-379 CODEN: GNMCEP; ISSN: 0888-7543
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **eph**-related receptors are the largest subfamily of receptor tyrosine kinases. Recently, we and others have identified seven

different, but related, cDNAs encoding membrane-bound ligands for this family of receptors. One member, LERK-7, is attached to the cell membrane via glycosyl-phosphatidylinositol linkage and has been found to be a ligand for the **eph**-family receptors **hek**, elk, **eck**, and rek. Using PCR-based screening of human .times. rodent somatic cell hybrid DNAs, we have assigned the gene that encodes LERK-7 (EPLG7) to human chromosome 5. Fluorescence in situ hybridization to metaphase chromosome prepns. using a genomic clone from the locus refined this localization to chromosome 5, band q21. In addn., Southern blot anal. of DNAs from interspecific backcross mice indicated that the mouse homolog Epl7 maps to a homologous region on chromosome 17.

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